II. REMARKS

Formal Matters

Claims 1-28 are pending after entry of the amendments set forth herein.

Claims 1-14 were examined and were rejected. Claim 15 was withdrawn from consideration.

Claims 1, 4-7, 11, 12, and 14 are amended. The amendments to the claims were made solely in the interest of expediting prosecution, and are not to be construed as acquiescence to any objection or rejection of any claim. Support for the amendments to claims 1, 4-7, 11, 12, and 14 is found in the claims as originally filed, and throughout the specification, in particular at the following exemplary locations: paragraph 0019; and paragraphs 0033, 0037, 0038, 0045, 0047, and 0052. Accordingly, no new matter is added by these amendments.

Claims 16-28 are added. Support for new claims 16-28 is found in the claims as originally filed, and throughout the specification, including the following exemplary locations: claims 16, 17, 21, 26, and 27: paragraphs 0019, 00148, and 00154; claim 20: 0033, 0037, 0038, 0045, 0047, and 0052. Accordingly, no new matter is added by these new claims.

Applicants respectfully request reconsideration of the application in view of the remarks made herein.

Restriction requirement

The Office Action set out a restriction requirement as follows:

Group I: claims 1-14; and

Group II: claim 15.

A provisional election of Group I claims was made without traverse. Applicants hereby confirm the election of Group I (claims 1-14) for prosecution on the merits.

Rejection under 35 U.S.C.§112, first paragraph

Claims 1-14 were rejected under 35 U.S.C.§112, first paragraph, as allegedly lacking enablement. Claims 1-14 were rejected under 35 U.S.C.§112, first paragraph, as allegedly failing to comply with the written description requirement.

Enablement

The Office Action stated that the specification does not reasonably provide enablement for a method of detecting an amyloid peptide-related neurological disorder, or a method of identifying a candidate agent for treating an amyloid peptide-related neurological disorder, comprising detecting a level of any calcium-responsive gene product in the brain of any non-human animal model. Applicants respectfully traverse the rejection.

The law regarding enablement of inventions is clear: "[t]he test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation."[1]

To aid in determinations of enablement, courts have identified eight factors for consideration: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill of those in the art; (g) the predictability or unpredictability of the art; and (h) the breadth of the claims.[2]

Calcium-responsive gene product

The Office Action indicated that the instant claims are enabled for methods involving detecting a level of calbindin mRNA, calbindin protein, neuropeptide Y mRNA, neuropeptide Y (NPY) protein, α-actinin II mRNA, and α-actinin II protein.

The specification provides *working examples* of **four** calcium-responsive gene products whose levels are altered in an animal model of an amyloid peptide-related neurological disorder. The four calcium-responsive gene products for which working examples are presented are c-fos, calbindin, neuropeptide Y, and α-actinin-II. A person skilled in the art would find it reasonable that the levels of other calcium-responsive gene products are affected in amyloid peptide-related neurological disorders.

Furthermore, while there may be some calcium-responsive gene products whose levels are not affected in an amyloid peptide-related neurological disorder, the courts have clearly taught that the specification does not have to disclose every species of a genus that would work and every species that would not work.

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[1] *United States v. Telectronics, Inc.*, 8 USPQ 2d 1217, 1233 (Fed. Cir. 1988), *cert. denied*, 490 U.S. 1046 (1989). See also *Genentech, Inc. v. Novo Nordisk*, 42 USPQ 2d 1001 (Fed. Cir. 1997), *cert. denied*, 522 U.S. 963 (1997); *Scripps Clinic and Research Foundation v. Genentech, Inc.*, 18 USPQ 2d 1001 (Fed. Cir. 1991).

[2] *Ex Parte Forman.*, 230 USPQ 546, 547 (Bd.Pat.App & Interf. 1986); and, *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The court has very clearly explained[3]:

> "To require such a complete disclosure would apparently necessitate a patent application or applications with thousands of catalysts....More importantly, such a requirement would force an inventor seeking adequate patent protection to carry out a prohibitive number of actual experiments. This would tend to discourage inventors from filing patent applications in an unpredictable area since the patent claims would have to be limited to those embodiments which are expressly disclosed. A potential infringer could readily avoid literal infringement of such claims by merely finding another analogous catalyst complex which could be used ...."

Since one of skill in the art would find it reasonable that the levels of calcium-responsive gene products other than c-fos, calbindin, NPY, and α-actinin II are affected in amyloid peptide-related neurological disorders, and since every species in a genus does not have to be tested for a genus to be enabled, extensive disclosure or guidance for every species of a genus does not have to be provided for a genus of this scope to be enabled.

The instant specification provides details as to how to carry out a subject method, e.g., how to detect a level of a calcium-responsive gene product. Specification, paragraphs 0036-0059. Given the guidance in the instant specification, along with the knowledge in the art, those skilled in the art could, without undue experimentation, carry out the claimed methods.

The courts have clearly taught that the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. For example, see MPEP §2164.01.[4]

As the court explained[5]:

> "[A] considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed."

Practitioners in the chemical and molecular biology arts frequently engage in extensive modification of reaction conditions and complex and lengthy experimentation where many factors must be varied to succeed in performing an experiment or in producing a desired result. The Federal Circuit has found that such extensive experimentation is not undue in the molecular biology arts. For example,

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[3] *In re Angstadt*, 190 USPQ 214, at 219 (CCPA 1976)
[4] See also *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 227 USPQ 428 (Fed. Cir. 1985).
[5] *In re Wands* 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)

the court concluded that extensive screening experiments, while being voluminous, were not undue in view of the art which routinely performs such long experiments.[6] The only experiments, if any, that need be performed to enable the entire scope of the claim are those designed to determine whether the level of a given calcium-responsive gene product is altered in an amyloid peptide-related neurological disorder. The specification provides ample detail, including working examples, of how to carry out such experiments. Since these experiments are routine in nature, no undue experimentation is required.

Animal model

The Office Action stated that the specification fails to disclose any animal model other than transgenic $hAPP_{FAD}/A\beta$ mice to be used in the claimed methods. However, the specification provides references to a number of transgenic animal models of amyloid peptide-related neurological disorders. Specification, paragraph 0069. The specification indicates that amyloid peptide-related neurological disorders include, but are not limited to, Alzheimer's Disease (AD), Parkinson's disease, and Lewy body disease; and includes cognitive impairments associated with AD, including impairment of learning ability, and memory impairment. Specification, paragraph 0019.

The animal models described in the publications listed in paragraph 0069 include transgenic mice comprising a human apolipoprotein-E (apoE) transgene (e.g., U.S. Patent Nos. 5,767,337 and 6,046,381), as well as transgenic mice comprising an APP or an Aβ transgene (e.g., U.S. Patent Nos. 6m175m957 and 6,455,757; and Rockenstein et al., Mucke et al., and Masliah et al., referred to in paragraph 0069). These references describe animal models of amyloid peptide-related neurological disorders such as AD. There is no requirement that the animal model of the amyloid peptide-related neurological disorder comprise a transgene encoding a mutant APP.

The specification provides sufficient enablement such that one of ordinary skill in the art would be able to practice the invention without undue experimentation. Accordingly, the instant claims meet the enablement requirement of 35 U.S.C.§112, first paragraph.

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[6] *Hybritech v. Monoclonal Antibodies, Inc.* 231 USPQ 81 (Fed. Cir. 1986)

Written description

The Office Action stated that the specification "teaches only the gene products of CB, c-Fos, neuropeptide Y, and α-actinin II are affected in level in response to expression of amyloid peptide." Office Action, page 13. The Office Action stated that in analyzing whether the written description requirement is met, it is first determined whether a representative number of species have been described; and stated that in the instant application, "only four genes have been disclosed." Office Action, page 13. This is not correct.

The instant application provides working examples of four calcium-responsive gene products whose levels are altered in amyloid peptide-related neurological disorders. These are just the working examples. The specification states that a calcium-responsive gene product refers to a protein and/or an mRNA whose level varies with the intracellular calcium ion concentration ($[Ca^{2+}_i]$). Specification, paragraph 0021. Applicants submit that a description of the four species discussed in the working examples is sufficient to satisfy the written description requirement. Indeed, as set forth in the MPEP §2163 II(A)(3)(a)(ii), there may be situations in which one species adequately supports a genus, and what constitutes a "representative number" is an inverse function of the skill and knowledge in the art. Here, Applicants have provided a description of a genus, and have provided a description of at least five species. As such, the written description requirement of 35 U.S.C.§112, first paragraph, has been satisfied.

Conclusion as to the rejections under 35 U.S.C.§112, first paragraph

Applicants submit that the rejection of claims 1-14 under 35 U.S.C. §112, first paragraph, has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

Rejection under 35 U.S.C.§102(b)

Claims 1, 3-8, and 10-14 were rejected under 35 U.S.C.§102(b) as allegedly anticipated by Vezzani et al. ((2002) *Neurosci.* 110:237-243; "Vezzani").

The Office Action stated that Vezzani teaches that neuropeptide Y (NPY) is a peptide widely distributed in various forebrain areas; that Vezzani teaches transgenic rats overexpressing the rat NPY gene have impaired spatial learning phenotype; and that Vezzani teaches that NPY mRNA levels were significantly increased in CA1 pyramidal neurons of NPY transgenic rats compared to wild-type rats. The Office Action stated that Vezzani anticipates claims 1, 3-8, and 10-14. Applicants respectfully

traverse the rejection.

Vezzani neither discloses nor suggests a method for detecting an amyloid peptide-related neurological disorder in a non-human animal model of the disorder. Vezzani neither discloses nor suggests a method for identifying a candidate agent for treating an amyloid peptide-related neurological disorder. Vezzani discusses a transgenic rat that overexpresses NPY. The NPY transgenic rat discussed in Vezzani is not an animal model for an amyloid peptide-related neurological disorder. Accordingly, Vezzani cannot anticipate any of claims 1, 3-8, and 10-14.

Furthermore, Vezzani does not disclose nor suggest a method of identifying a candidate agent for treating an amyloid peptide-related neurological disorder. Vezzani discusses administering kainic acid to an NPY transgenic rat. Kainic acid is not considered a candidate agent for treating an amyloid peptide-related neurological disorder. Kainic acid induces hippocampal seizures. A disclosure of administering a compound that induces hippocampal seizures does not anticipate a method of identifying a candidate agent for treating an amyloid peptide-related neurological disorder.

Still further, Vezzani does not disclose or suggest that NPY overexpression is indicative of an amyloid peptide-related neurological disorder. Instead, Vezzani states that seizure susceptibility and epileptogenesis are decreased in transgenic rats overexpressing NPY.

Applicants submit that the rejection of claims 1, 3-8, and 10-14 under 35 U.S.C. §102(b) has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

Rejection under 35 U.S.C.§103(a)

Claims 2 and 9 were rejected under 35 U.S.C.§103(a) as allegedly unpatentable over Lamb et al. ((1997) *Human Molecular Genetics* 6:1535-1541; "Lamb") in view of Vezzani.

The Office Action stated that: 1) Lamb teaches that Alzheimer's Disease (AD) has several genetic etiologies, including mutations in the beta-amyloid precursor protein (APP) gene; 2) Lamb does not teach a method of detecting an amyloid peptide-related neurological disorder and a method of identifying a candidate agent for treating an amyloid peptide-related neurological disorder in a transgenic non-human animal model of AD comprising $hAPP_{FAD}/A\beta$; 3) Vezzani teaches transgenic rats

overexpressing NPY; and 4) Vezzani teaches that increased NPY mRNA levels in granule neurons occurred after kainic acid treatment. The Office Action stated that it would have been obvious to modify the methods of Lamb and Vezzani to detect an amyloid peptide-related neurological disorder or to identify a candidate agent for treating an amyloid peptide-related neurological disorder in a transgenic non-human animal model of AD "given the motivation provided by Lamb teaching the significance of using tg mice comprising $hPAPP_{FAD}/A\beta$ to screen for therapeutic agents in view of the motivation provided by Vezzani teaching that NPY tg rats have an impaired spatial learning phenotype do [sic] to an increase in NPY mRNA and peptide levels." Office Action, page 18. Applicants respectfully traverse the rejection.

Lamb states that the transgenic mice discussed therein should provide valuable for testing therapeutic agents that specifically alter APP metabolism and Aβ production. Lamb, Abstract. However, Lamb neither discloses nor suggests a method of detecting an amyloid peptide-related neurological disorder, or a method of identifying a candidate agent for treating an amyloid peptide-related neurological disorder, where the methods involve detecting a level of a calcium-responsive gene product in brain tissue of an animal model of an amyloid peptide-related neurological disorder.

Vezzani does not cure the deficiency of Lamb. Vezzani does not teach that NPY transgenic rats have impaired spatial learning. Instead, Vezzani states that seizure susceptibility and epileptogenesis are decreased in transgenic rats overexpressing NPY. Seizures, e.g., epileptic seizures, are not amyloid peptide related neurological disorders.

There is no disclosure or suggestion in Lamb, alone or in combination with Vezzani, to detect an amyloid peptide-related neurological disorder, or to identify a candidate agent for treating an amyloid peptide-related neurological disorder, where the method involves detecting a level of a calcium-responsive gene product in an animal model of the disorder. Accordingly, Lamb, alone or in combination with Vezzani, cannot render claims 2 and 9 obvious.

Applicants submit that the rejection of claims 2 and 9 under 35 U.S.C. §103(a) has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

III. CONCLUSION

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number UCAL-280.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: Feb. 9, 2006

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